

*D1* *Cont* ACCGGCCTTTCGCGGTGA or 5'-GTGCACGGAAAGGTGCAGGCCACACT (SEQ ID NOS: 24-26).

➤ On Page 47, please replace lines 13-18 with the following text:

In an exemplary embodiment, portions of the 5' flanking region of the human Shh gene are amplified using primers which add restriction sites, to generate the following fragments

*D2* 5'-gcgcgccttcgaaGCGAGGCAGCCAGCGAGGGAGAGAGCGAGCGGGCGAGCCGGAGC-GAGGAAatcgatgcgcgc (primer 1) (SEQ ID NO: 21)

5'-gcgcgcagatctGGGAAAGCGCAAGAGAGAGCGCACACGCACACACCCGCCGCGCG-CACTCGgatccgcgcgc (primer 2) (SEQ ID NO: 22)

➤ On Page 48, please replace lines 1-20 with the following text:

Individual colonies are selected, cut with *Asu*II and *Bam*HI, and the size of the *Asu*II/*Bam*HI fragment determined. Colonies in which both the primer-1 and primer-2 sequences are correctly inserted are further amplified, and cut with *Asu*II and *Bam*HI to produce the gene activation construct:

*D3* cgaagcgaggcagccagcgagggagagagcgagcgggagcgagccggagcgaggaaATCGAAGGTT  
CGAATCCTTCCCCACCACCATCACTTTCAAAGTCCGAAAGAATCTGCTCCCTGCTTGTGTGT  
TGGAGGTCGCTGAGTAGTGCGCGAGTAAAATTTAAGCTACAACAAGGCAAGGCTTGACCGACAA  
TTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCGCGATGTACGGGCCAGATAT  
ACGCGTTGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATA  
GCCCATATATGGAGTTCCGCGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAA  
CGACCCCCGCCCATTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTC  
CATTGACGTCAATGGGTGGACTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATC  
ATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCA  
GTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACC  
ATGGTGATGCGGTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTC  
CAAGTCTCCACCCCATTGACGTCAATGGGAGTTTGTGTTTGGCACCAAAATCAACGGGACTTTC  
AAAATGTCGTAACAACCTCCGCCCCATTGACGCAAATGGGCGGTAGGCGGTGTACGGTGGGAGGTC  
TATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTATCGAAATTAATA  
CGACTCACTATAGGGAGACCCAAGCTTGGTACCGAGCTCGGATCgatctgggaaagcgcaagag  
agagcgcacacgcacacacccgccgcgcgactcgg (SEQ ID NO: 23)

➤ On Page 62, please replace lines 16-21 with the following text:

In an illustrative embodiment, the *ptc* therapeutic can be an antisense construct for inhibiting the expression of *patched*, e.g., to mimic the inhibition of *patched* by *hedgehog*. Exemplary antisense constructs include:

D<sup>4</sup> 5'-GTCCTGGCGCCGCGCCGCGCGTCGCC (SEQ ID NO: 24)

5'-TTCCGATGACCGGCCTTTCGCGGTGA (SEQ ID NO: 25)

5'-GTGCACGGAAAGGTGCAGGCCACACT (SEQ ID NO: 26)

*The replacement paragraphs presented above incorporates changes as indicated by the marked-up versions below.*

In yet other embodiments of the present invention, the *ptc* therapeutic alters the level of expression of a *hedgehog* protein, a *patched* protein or another protein involved in the intracellular signal transduction pathway of *patched*. In this regard, the *ptc* therapeutic can be an antisense construct which inhibits the expression of a protein which is involved in the signal transduction pathway of *patched* and the expression of which antagonizes *hedgehog*-mediated signals. For example, the antisense molecule can be one which hybridizes to a *patched* transcript or genomic sequence, such as 5'-GTCCTGGCGCCGCGCCGCGCGTCGCC, 5'-TTCCGATG-ACCGGCCTTTCGCGGTGA or 5'-GTGCACGGAAAGGTGCAGGCCACACT (SEQ ID NOS: 24-26).

In an exemplary embodiment, portions of the 5' flanking region of the human *Shh* gene are amplified using primers which add restriction sites, to generate the following fragments  
5'-gcgcgcttcgaaGCGAGGCAGCCAGCGAGGGAGAGAGCGAGCGGGCGAGCCGGAGC-  
GAGGAAatcgatgcgcg (primer 1) (SEQ ID NO: 21)  
5'-gcgcgcgagatctGGGAAAGCGCAAGAGAGAGCGCACACGCACACACCCGCCGCGCG-  
CACTCGggatccgcgcg (primer 2) (SEQ ID NO: 22)

Individual colonies are selected, cut with *Asu*II and *Bam*HI, and the size of the *Asu*II/*Bam*HI fragment determined. Colonies in which both the primer 1 and primer 2 sequences

are correctly inserted are further amplified, and cut with *AsuII* and *BamHI* to produce the gene activation construct:

cgaagcgagggcagccagcgaggggagagagcgagcgggcgagccggagcgaggaaATCGAAGGTT  
 CGAATCCTTCCCCACCACCATCACTTTCAAAAGTCCGAAAGAATCTGCTCCCTGCTTGTGTGT  
 TGGAGGTCGCTGAGTAGTGCGCGAGTAAATTTAAGCTACAACAAGGCAAGGCTTGACCGACAA  
 TTGCATGAAGAATCTGCTTAGGGTTAGGCGTTTTGCGCTGCTTCGCGATGTACGGGCCAGATAT  
 ACGCGTTGACATTGATTATTGACTAGTTATTAATAGTAATCAATTACGGGGTCATTAGTTCATA  
 GCCCATATATGGAGTTCGCGGTTACATAACTTACGGTAAATGGCCCGCCTGGCTGACCGCCCAA  
 CGACCCCGCCCATTTGACGTCAATAATGACGTATGTTCCCATAGTAACGCCAATAGGGACTTTC  
 CATTGACGTCAATGGGTGGACTATTTACGGTAAACTGCCCACTTGGCAGTACATCAAGTGTATC  
 ATATGCCAAGTACGCCCCCTATTGACGTCAATGACGGTAAATGGCCCGCCTGGCATTATGCCCA  
 GTACATGACCTTATGGGACTTTCCTACTTGGCAGTACATCTACGTATTAGTCATCGCTATTACC  
 ATGGTGATGCGGTTTTTGGCAGTACATCAATGGGCGTGGATAGCGGTTTGACTCACGGGGATTTT  
 CAAGTCTCCACCCCATTTGACGTCAATGGGAGTTTGTGTTTGGCACCAAAATCAACGGGACTTTCC  
 AAAATGTCGTAACAACCTCCGCCCCATTGACGCAAATGGGCGGTAGGCGTGTACGGTGGGAGGTC  
 TATATAAGCAGAGCTCTCTGGCTAACTAGAGAACCCACTGCTTACTGGCTTATCGAAATTAATA  
 CGACTCACTATAGGGAGACCCAAGCTTGGTACCGAGCTCGGATCgatctgggaaagcgcaagag  
 agagcgcacacgcacacacccgcccgcgcgcactcgg (SEQ ID NO: 23)

In an illustrative embodiment, the *ptc* therapeutic can be an antisense construct for inhibiting the expression of *patched*, e.g., to mimic the inhibition of *patched* by *hedgehog*. Exemplary antisense constructs include:

5'-GTCCTGGCGCCGCGCCGCGCGTCGCC (SEQ ID NO: 24)

5'-TTCCGATGACCGGCCTTTCGCGGTGA (SEQ ID NO: 25)

5'-GTGCACGGAAAGGTGCAGGCCACACT (SEQ ID NO: 26)

#### IN THE CLAIMS:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.